REMARKS

Applicants acknowledge the current status of the claims, as reported in Office Action dated 31 December 2002. Claims 1-88 are pending; restriction of the claims has been made final and claims 5-8, 11, and 32-88 are withdrawn from consideration; and claims 1-4, 9,10 and 12-31 are under consideration.

Applicants note the Examiner's consideration in full of Applicant's information disclosure statement. Applicants apologize for the inadvertent omission of pages from the cited art as noted by the Examiner, and thank the Examiner for obtaining the complete documents for purposes of consideration.

The specification is amended to acknowledge the proprietary nature of the disclosed trademark, "BIACORE."

Claims 1, 4, 9 and 31 are amended to recite more precisely the nature of what Applicants claim as their invention and to avoid latent ambiguity of the claim language.

Specifically claims 1 and 4 have been amended to recite Applicant's dual specific antibody is not a fully mouse antibody. Support for these amendments can be found throughout the specification as filed, and particularly at pages 29-30. No new matter is added.

Claim 9 is amended by deleting the phrase "designed based on" and inserting therefor the phrase "made by." This amendment is supported in the specification as filed at page 3, lines 10-14. No new matter is added.

Claim 31 is amended to clarify the nature of the product obtainable by the method of claim 4 by inserting the clause "said dual-specificity antibody, or antigen-binding portion thereof." This amendment is supported in the specification as filed at page 4, lines 31-32. No new matter is added.

New claims

New claims 89-95 are introduced herein to recite specifically preferred embodiments of Applicants' claimed dual-specificity antibody, or antigen-binding portion thereof that specifically binds interleukin-1α and interleukin-1β as taught in the specification as filed.

New claim 89 is directed to a dual-specificity antibody, or antigen-binding portion thereof, wherein said dual-specificity antibody, or antigen-binding portion is fully human. Support for this claim is found throughout the specification as filed, particularly at page 29, lines 11-30. No new matter is introduced.

New claims 90 and 91are directed to a dual-specificity antibody, or antigen-binding portion thereof, wherein said dual-specificity antibody, or antigen-binding portion is chimeric. Support for these claims is found throughout the specification as filed, particularly at page 30, lines 16-19. No new matter is introduced.

New claims 92, 93, and 94 are directed to a dual-specificity antibody, or antigen-binding portion thereof, wherein said dual-specificity antibody, or antigen-binding portion is CDR grafted. Support for these claims is found throughout the specification as filed, particularly at page 30, lines 20-25. No new matter is introduced.

New claim 95 is directed to a dual-specificity antibody, or antigen-binding portion thereof, wherein said dual-specificity antibody, or antigen-binding portion is humanized. Support for this claim is found throughout the specification as filed, particularly at page 30, lines 26-32. No new matter is introduced.

Attached hereto as **Appendix A** is a marked-up version of the changes made to the specification by amendment under 37 CFR §1.121(b)(1)(iii). Also attached hereto as **Appendix B** is a marked-up version of the changes made to the claims by amendment under 37 CFR § 1.121(c)(1)(i). Reconsideration and allowance of the pending claims in light of the foregoing amendments and the following remarks are respectfully requested.

Specification

In the Office Action at page 3, paragraph 3, the specification is objected to as improperly citing the trademark BIAcore™ and without accompanying generic terminology.

Applicants have amended the specification at page 31, line 4 and page 32, line 3 by replacing the term "BIAcore" with "BIACORE". In the specification as filed, at page 31, lines 3-5, immediately preceding the term BIACORE, the BIACORE bioassay is specifically described as detecting "real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix,." In addition, Applicants have amended the specification, adding the term "bioassay" as a generic descriptor of the BIACORE trademark. No new matter is added.

Rejection under 35 USC §102(b)

In the Office Action, at page 4, paragraph 5, claims 1-4, 12-14, and 31 are rejected under 35 USC §102(b) as being anticipated by Kock et al., J. Exp. Med., 1986, Vol.163, no.2, pp. 463-468 and Luger et. al., Immunobiology, 1986, vol. 172, pp. 346-356. The Examiner asserts that Kock et al., and Luger et al., each teach a monoclonal antibody that reacts with, and inhibits, the activity of both interleukin-1α (IL-1α) and interleukin-1β (IL-1β).

For purposes of advancing examination of the present application to allowance only, Applicants have amended claims 1 and 4 to recite that Applicant's dual-specificity antibody, or antigen-binding portion thereof, that specifically binds interleukin-1α and interleukin-1β is not fully mouse antibody.

Support for dual-specificity antibodies other than mouse antibodies can be found throughout the specification as filed and particularly at pages 29-30. Furthermore, negative limitations, or claim exclusion by proviso, is proper patent practice, provided such limitations are sufficiently definite (see MPEP 2173.05(i)). Applicants assert the recited antibodies are sufficiently definite and the boundaries of the patent protection sought are sufficiently clear to render Applicant's negative limitation proper. (See also *In re Wakefield*, 422 F.2d 897, 899, 904, 164 USPQ 636, 638, 641 (CCPA 1970). *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971). *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977).). Applicants reserve the right to prosecute excluded subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Applicant's invention, as amended, is directed to a dual-specificity antibody that can bind both IL-1α and IL-1β, and a method of making such a dual-specificity antibody wherein the dual-specificity antibody is not fully mouse.

Luger et al. and Kock et al. disclose a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Neither Luger et al. nor Kock et al. teach or suggest a dual-specificity antibody that can bind both IL-1α and IL-1β and is not a fully mouse antibody (e.g., chimeric antibodies, CDR grafted antibodies, humanized antibodies and fully human antibodies).

Luger et al. and Kock et al do not teach or suggest each and every element of the present invention either expressly or inherently; i.e., a dual-specificity antibody which is not a fully mouse antibody capable of binding both IL-1α and IL-1β. Because neither cited reference teach or suggest dual-specificity antibodies comprising non-mouse immunoglobulin regions, it fails to anticipate Applicants' invention.

In view of Applicants' claim amendments, Applicants submit the present invention as claimed is patentable over the Luger et al. and Kock et al. disclosures. Applicants therefore respectfully request removal of the rejection of claims 1-4, 12-14 and 31under 35 USC §102(b).

Rejections under 35 USC §103(a)

In the Office Action, at page 5, paragraph 7, claims 16, 28, and 29 are rejected under 35 USC §103(a) as being unpatentable over Luger et al.in view of Green, J.Immunological Methods 1999, Vol. 231, pp. 11-23. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Green with those of Luger et al. to produce humanized or chimeric antibodies to IL-1. Applicants respectfully disagree.

BASIC REQUIREMENTS OF A *PRIMA FACIE* CASE OF OBVIOUSNESS

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations.
>
> MPEP §2143

It is well recognized that:

> Hindsight reconstruction of a claimed invention, absent a teaching or suggestion in the art is impermissible.
>
> MPEP §2142

As amended, Applicant's claimed invention is directed to a dual-specificity antibody, or antigen binding portion thereof to IL-1α and IL-1β wherein the antibody or antigen binding portion is not fully mouse. Claims 16, 28 and 29 recite specific aspects of Applicant's invention wherein Applicant's dual-specificity antibody is a human antibody generated from a transgenic mouse (claim 16); is a fully human antibody (claim 28); or is a chimeric antibody (claim 29).

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. The Examiner acknowledges that Luger et al. do not teach the use of transgenic mice for the production of human or chimeric antibodies.

Green teaches the use of transgenic mice that generate human antibodies. However, as the Examiner acknowledges, Green does not teach or suggest a method of making of making a dual-specificity antibody to IL-1α and IL-1β. In addition, Green does not teach or suggest chimeric, humanized or human dual-specificity antibodies to IL-1α and IL-1β.

The Examiner asserts that one of ordinary skill in the art would have been reasonably expected to combine the teaching of Luger et al. with those of Green to produce humanized IL-1 antibodies or chimeric antibodies. The Examiner asserts that one of ordinary skill in the art would expect to be able to produce a superior monoclonal antibody for use in inhibiting IL-1 in inflammation. Neither Luger et al. nor Green, either singularly or in combination, teach or suggest the use of a mouse transgenic for human antibody genes to generate human or chimeric dual-specificity antibodies to IL-1α and IL-1β.

As amended, Applicant's claimed invention is directed to a dual-specificity antibody, or antigen binding portion thereof to IL-1α and IL-1β wherein the antibody or antigen binding portion is not fully mouse. Applicants have taught how to generate antigens to generate dual-specificity antibodies. (see

pages 7-11 and pages 47-49 of specification as filed). One of Applicant's preferred embodiments is directed to the use of transgenic mice for generating chimeric or human dual-specificity antibodies to IL-1α and IL-1β. (see page 15, line 20-page 16, line 11 of specification as filed). The Examiner has used Applicants' disclosure as a template to search and reconstruct Applicants' invention. In one aspect, the Examiner has searched for, and subsequently cited Luger et al. as disclosing a fully mouse monoclonal antibody that binds IL-1α and IL-1β. In a separate aspect, the Examiner has searched for and cited Green as disclosing transgenic mice capable of generating human antibodies. Luger et al. do not teach or suggest the use of transgenic animals. Green does not teach or suggest the generation of dual-specificity antibodies. The combination of the cited art is made only by the Examiner, upon guidance, direction, and motivation to do so by Applicants' present invention. This is hindsight reconstruction and is impermissible as a basis for rejection under 35 USC §103.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use a mouse transgenic for human antibody genes to generate a human or chimeric dual-specificity antibody to IL-1α and IL-1β. Instead, the Examiner has employed impermissible hindsight to fabricate a case of obviousness.

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 16, 28, and 29 as obvious under 35 USC §103(a), and in view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 16, 28, and 29 under 35 USC §103(a).

The Examiner has repeatedly rejected claims for the present application as obvious based upon improper and impermissible hindsight reconstruction by piecing together separate and disparate publications in an effort to patchwork-fabricate Applicant's claimed invention. In each case, Applicants assert there is no suggestion or motivation, to modify or to combine reference teachings except for Applicant's present disclosure. Applicants now address each of these rejections in turn.

In the Office Action, at page 6, paragraph 8, claims 17 and 28 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of Nguyen et al., Microbiol Immunol.1997, Vol. 41(12), 231, pp. 901-907. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Nguyen et al., with those of Luger et al. to produce dual-specificity human antibodies to IL-1α and IL-1β using SCID mice reconstituted with human peripheral blood lymphocytes. Applicants respectfully disagree.

Claims 17 and 28 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by immunizing a SCID mouse that has been reconstituted with human peripheral blood mononuclear cells or lymphoid cells.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach the use of SCID mice reconstituted with human peripheral blood lymphocytes for the production of human antibodies.

Nguyen et al., teach the use of SCID mice reconstituted with human peripheral blood lymphocytes for the production of human antibodies. Nguyen et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use SCID mice reconstituted with human peripheral blood lymphocytes to generate a human dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Nguyen et al., either singularly or in combination, teach or suggest the use of a SCID mouse reconstituted with human peripheral blood lymphocytes to generate a human dual-specificity antibody to IL-1α and IL-1β. Instead, the Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Nguyen.

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 17 and 28 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 17 and 28 under 35 USC §103(a).

In the Office Action, at page 6, paragraph 9, claims 18 and 28 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of Reisner et al., Tibtech,1998, Vol. 16, 231, pp. 242-246. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Reisner et al., with those of Luger et al. to produce dual-specificity human antibodies to IL-1α and IL-1β using a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with human lymphocytes. Applicants respectfully disagree.

Claims 18 and 28 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by immunizing a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with functional human lymphocytes.

Luger et al. teach a fully mouse monoclonal antibody that reacts with IL-1α and IL-1β. Luger et al. do not teach the use of a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with functional human lymphocytes for the production of human antibodies.

Reisner et al., teach the use of a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with functional human lymphocytes for the production of human antibodies. Reisner et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with functional human lymphocytes to generate a human dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Reisner et al., either singularly or in combination, teach or suggest the use of a mouse treated with lethal total body irradiation, followed by radioprotection with bone marrow cells of a SCID mouse, followed by engrafment with functional human lymphocytes to generate a human dual-specificity antibody to IL-1α and IL-1β. As with the rejections discussed supra, the Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Reisner et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 18 and 28 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 18 and 28 under 35 USC §103(a).

In the Office Action, at page 7, paragraph 10, claims 19, 20 and 24 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of Barbas et al., Proc. Nat. Acad. Sci. 1991, Vol. 88, pp. 7978-7982. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Barbas et al., with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β using phage display. Applicants respectfully disagree.

Claims 19, 20 and 24 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by screening a recombinant antibody library with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach screening of recombinant antibody libraries for the production of antibodies.

Barbas et al., teach the use of combinatorial (recombinant) antibody libraries on phage surfaces to generate antibodies in vitro. Barbas et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use recombinant antibody libraries to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Barbas et al., either singularly or in combination, teach or suggest the use of recombinant antibody libraries to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Barbas et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 19, 20 and 24 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 19, 20 and 24 under 35 USC §103(a).

In the Office Action, at page 8, paragraph 11 claims 19 and 21 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of WO 99/36569, Wittrup et al., 1999. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Wittrup et al., with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β using yeast display. Applicants respectfully disagree.

Claims 19 and 21 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by screening a recombinant antibody library displayed on the surface of yeast with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach screening of recombinant antibody libraries displayed on the surface of yeast cells for the production of antibodies.

Wittrup et al., teach the use of recombinant antibody libraries displayed on yeast cell surfaces to generate antibodies in vitro. Wittrup et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to

combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use recombinant antibody libraries displayed on the surface of yeast cells to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Wittrup et al., either singularly or in combination, teach or suggest the use of recombinant antibody libraries to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Wittrup et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 19 and 21 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 19 and 21 under 35 USC §103(a).

In the Office Action, at page 8, paragraph 12, claims 19, 21 and 22 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of WO 98/49286, Iverson et al., 1998. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Iverson et al., with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β using yeast display and display on bacterial cells. Applicants respectfully disagree.

Claims 19, 21 and 22 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by screening a recombinant antibody library displayed on the surface of yeast or bacteria with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach screening of recombinant antibody libraries displayed on the surface of yeast cells or bacterial cells for the production of antibodies.

Iverson et al., teach the use of recombinant antibody libraries displayed on yeast cell surfaces or bacterial cells to generate antibodies in vitro. Iverson et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use recombinant antibody libraries displayed on the surface of yeast cells or bacterial cells to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Iverson et al., either singularly or in combination, teach or suggest the use of recombinant antibody libraries to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to

one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Iverson et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 19, 21and 22 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 19, 21and 22 under 35 USC §103(a).

In the Office Action, at page 9, paragraph 13, claims 19 and 23 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of WO 98/31700. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of WO 98/31700 with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β from recombinant libraries expressed as RNA-protein fusions. Applicants respectfully disagree.

Claims 19 and 23 recite specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by screening a recombinant antibody library expressed as RNA-protein fusions with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach screening of recombinant antibody libraries expressed as RNA-protein fusions for the production of antibodies.

WO 98/31700 teaches the use of recombinant antibody libraries expressed as RNA-protein fusions to generate antibodies in vitro. WO 98/31700 does not contain any teaching or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use recombinant antibody libraries expressed as RNA-protein fusions to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor WO 98/31700 publication, either singularly or in combination, teach or suggest the use of recombinant antibody libraries expressed as RNA-protein fusions to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth in WO 98/31700.

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 19, and 23 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 19 and 23 under 35 USC §103(a).

In the Office Action, at page 9, paragraph 14, claim 25 is rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of US Patent 5,580,717, Dower et al., 1996. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Dower et al.with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β from large recombinant libraries. Applicants respectfully disagree.

Claim 25 recites specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by exposing the antibody repertoire to antigen in vivo followed by screening a recombinant antibody library, prepared from lymphoid cell of the animal, with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach screening of recombinant antibody libraries for the production of antibodies.

Dower et al.teaches the use of recombinant antibody libraries to generate antibodies in vitro. Dower et al.do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use recombinant antibody libraries to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Dower et al.either singularly or in combination, teach or suggest the use of recombinant antibody libraries to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Dower et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claim 25 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claim 25 under 35 USC §103(a).

In the Office Action, at page 10, paragraph 15, claim 26 is rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of WO 97/29131, Salfeld et al., 1997. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Salfeld et al. with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β by in vitro affinity maturation. Applicants respectfully disagree.

Claim 26 recites specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by in vitro affinity maturation of a recombinant antibody library prepared

from lymphoid cells of an animal previously immunized with the antigen and identifying a dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach the use of in vitro affinity maturation of a recombinant antibody library prepared from lymphoid cells of an animal previously immunized with the antigen to generate antibodies.

Salfeld et al., teach the use of in vitro affinity maturation of a recombinant antibody library prepared from lymphoid cells of an animal previously immunized with the antigen to generate TNFα antibodies. Salfeld et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to use in vitro affinity maturation of a recombinant antibody library prepared from lymphoid cells of an animal previously immunized with the antigen to generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Salfeld et al., either singularly or in combination, teach or suggest in vitro affinity maturation of a recombinant antibody library prepared from lymphoid cells of an animal previously immunized with the antigen to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Salfeld et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claim 26 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claim 26 under 35 USC §103(a).

In the Office Action, at page 10, paragraph 16, claim 27 is rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of Babcock et al., Proc. Nat. Acad. Sci. 1996, Vol. 93, pp. 7843-7848. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Babcock et al., with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β by selecting single cells secreting antibodies that bind the antigen from immunized animals. Applicants respectfully disagree.

Claim 27 recites specific aspects of Applicant's invention wherein a dual-specificity antibody to IL-1α and IL-1β is generated by immunizing animals with antigen and selecting single cells secreting antibodies that bind antigen and recovering heavy and light chain variable region cDNAs to generate libraries and use to generate dual-specificity antibody.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach selection of single cells secreting antibodies that bind antigen for the production of antibodies.

Babcock et al., teach the method of isolating single cells secreting antibodies that bind antigen to generate monoclonal antibodies. Babcock et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to select single cells secreting antibodies that bind antigen and recovering heavy and light chain variable region cDNA to generate recombinant antibody library and generate a dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Babcock et al., either singularly or in combination, teach or suggest selection of single cells secreting antibodies that bind antigen to generate dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Babcock et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claim 27 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claim 27 under 35 USC §103(a).

In the Office Action, at page 11, paragraph 17, claims 29 and 30 are rejected under 35 USC §103(a) as being unpatentable over Luger et al. in view of Knappik et al., JMB Feb. 2000, Vol. 296, pp. 57-86. The Examiner asserts that it would be obvious to one skilled in the art to combine the teachings of Knappik et al., with those of Luger et al. to produce dual-specificity antibodies to IL-1α and IL-1β by CDR grafting method. Applicants respectfully disagree.

Claims 29 and 30 recite specific aspects of Applicant's invention directed to a method of making a chimeric or CDR-grafted dual-specificity antibody to IL-1α and IL-1β.

Luger et al. teach a fully mouse monoclonal antibody which reacts with IL-1α and IL-1β. Luger et al. do not teach method of generating chimeric or CDR-grafted antibodies.

Knappik et al., teach the method of generating chimeric or CDR-grafted antibodies. Knappik et al., do not teach or suggest a method of making a dual-specificity antibody to IL-1α and IL-1β.

Applicants assert there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to

combine the reference teachings (required as the first criterion to establish a *prima facie* case of obviousness) to generate chimeric or CDR-grafted dual-specificity antibody to IL-1α and IL-1β. Neither Luger et al. nor Knappik et al., either singularly or in combination, teach or suggest the method of making chimeric or CDR-grafted dual-specificity antibody to IL-1α and IL-1β. The Examiner has employed impermissible hindsight, using Applicants' disclosure as a reconstruction template, to improperly assert that it would be obvious to one skilled in the art to produce a dual-specificity antibody to IL-1α and IL-1β using the approaches set forth by Knappik et al..

The cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 29 and 30 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 29 and 30 under 35 USC §103(a).

Finally, should the Examiner feel it necessary to maintain one or more of the preceding rejections under 35 USC §103, Applicants respectfully request that the Examiner direct the Applicant's attention to the specific passage(s) or other supporting art wherein suggestion or motivation to combine the cited art can be found.

Rejections under 35 USC §112, first paragraph

In the Office action at page 12, paragraph 2, claims 1-4, 9, and 12-31 are rejected under 35 USC §112, first paragraph to as allegedly containing subject matter which does not reasonably provide enablement for all dual-specificity antibodies and means of making them. Specifically, the Examiner asserts that Applicants have not described the characteristics of peptides that generate dual-specificity antibodies so that one of skill in the art could predictably identify other such peptides as broadly claimed. The Examiner asserts that it is not routine to screen large numbers of peptides that might potentially generate such antibodies where the expectation of obtaining similar specificity is unpredictable. Further, the Examiner asserts that no peptide other than the one containing the overlapping region of IL-1α and IL-1β are taught to be able to generate a dual-specificity antibody. Applicants respectfully disagree.

The MPEP §2164.06 in relevant part provides that:

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is

> merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. United States v. Telectronics Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

It is also recognized that:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).
>
> MPEP §2164.08(b)

Applicants teach how to make antigens. Applicants respectfully draw the Examiner's attention to pages 7-11 and pages 47-49 of the specification as filed. Applicants teach how to generated antibodies (see pages 11-31 of the specification as filed). Applicants teach how to screen and identify dual-specificity antibodies using binding assays (see pages 31-33 of the specification as filed).

Applicants respectfully submit that sufficient guidance is provided in the specification as filed that one of ordinary skill in the art would readily comprehend the structural features necessary to generate dual-specificity antibodies to IL-1α and IL-1β. Contrary to the Examiner's assertion that a large number of peptides will have to be screened to generate dual-specificity antibodies, Applicant's disclosure gives proper and sufficient guidance such that only a reasonable number of peptides will have to be screened to obtain dual-specificity antibodies to IL-1α and IL-1β with specificities described in the specification as filed. In addition, as stated above the quantity of experiments is not determinative for 'undue experimentation'. One of ordinary skill in the art will recognize that the amount of experimentation needed is routine and by no means undue.

From Applicant's disclosure, one of ordinary skill in the art can readily comprehend the structural features necessary to generate dual-specificity antibodies to IL-1α and IL-1β. Applicants respectfully submit that the presence of inoperative embodiments within the scope of the claims does not render the claims non-enabled. The Examiner acknowledges that Applicants provide a working example of a dual specificity antibody. Applicants further teach how one of ordinary skill in the art can make and

use additional embodiments of Applicant's invention. Accordingly, Applicants submit that one skilled in the art would recognize that Applicants, at the time of filing, were in possession of the claimed invention and that the specification as filed fully enables one skilled in the art.

In view of the foregoing amendment, Applicants respectfully request the removal of the rejection to claims 1-4, 9, and 12-31 under 37 USC §112 first paragraph.

Rejections under 35 USC §112, second paragraph

In the Office action at page 14, paragraph 1, claims 9 and 31 are rejected under 35 USC §112, second paragraph to as being indefinite for failing to claim the subject matter of Applicant's invention. Specifically the Examiner asserts:

A) Claim 9 is indefinite in the recitation of "...is designed based on...";

and

B) Claim 31 is indefinite because, as written, it is the IL-1 molecules that are obtainable by the method of claim 4.

Applicants have amended claims 9 and 31 to avoid latent ambiguities identified by the Examiner.

Applicants have amended claim 9 by deleting the phrase "designed based on" and inserting therefor "made by", such that the phrase now reads "antigen made by splicing overlapping portions of." This amendment is supported in the specification as filed, for example at page 3, lines 10-14. No new matter is added.

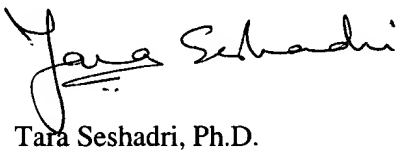
Applicants have amended claim 31 such that it is the antibody or antigen binding portion that is obtainable by the method of claim 4. This amendment is supported in the specification as filed at page 4, lines 31-32. No new matter is added.

In view of the foregoing amendment, Applicants respectfully request the removal of the rejection to claims 9 and 31 under 37 USC §112 second paragraph.

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that all objections and rejections set forth in the Office Action of 31 December 2002 have been avoided or overcome, and consequently the application is in condition for allowance. Reconsideration and removal of the rejections, and allowance of the pending amended claims are, therefore, respectfully requested.

Respectfully submitted,



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APPENDIX A

AMENDMENTS TO SPECIFICATION

UNDER 37 CFR §1.121(b)(1)(iii):

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please delete the paragraph starting at page 31, line 1 and insert the following therefor:

--One way of measuring the binding kinetics of an antibody is by surface plasmon resonance. The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the ~~BIAcore~~ BIACORE bioassay system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Jönsson, U., *et al.* (1993) *Ann. Biol. Clin.* 51:19-26; Jönsson, U., *et al.* (1991) *Biotechniques* 11:620-627; Johnsson, B., *et al.* (1995) *J. Mol. Recognit.* 8:125-131; and Johnnson, B., *et al.* (1991) *Anal. Biochem.* 198:268-277.

Please delete the paragraph starting at page 31, line 29, and insert the following therefor:

--The dual specificity antibodies of the invention may display equal binding activity toward the two different but structurally related antigens to which it binds or, alternatively, the dual specificity antibodies may bind more preferentially to one of the two antigens, yet still have specificity towards the two related antigens as compared to unrelated antigens. The binding activity of the dual specificity antibodies toward the structurally related antigens, as well as toward unrelated antigens, can be assessed using standard *in vitro* immunoassays, such as ELISA or ~~BIAcore~~ BIACORE bioassay analysis. Preferably, the ratio of K_d of antibody toward structurally unrelated antigens to the K_d of antibody toward structurally related antigens should be at least 3, even more preferably the ratio should be at least 5, even more preferably the ratio should be at least 10, or even more preferably the ratio should be at least 50, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000.--

APPENDIX B

CLAIM AMENDMENTS UNDER 37 CFR §1.121(c)(1)(ii):

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A dual-specificity antibody, or antigen-binding portion thereof, that specifically binds interleukin-1α and interleukin-1β, wherein said antibody is not a fully mouse antibody.

4. (Amended) A method of obtaining a dual-specificity antibody that specifically binds interleukin-1α and interleukin-1β, the method comprising:
providing an antigen that comprises a common structural feature of IL-1α and IL-1β;
exposing an antibody repertoire to the antigen; and
selecting from the repertoire an antibody that specifically binds IL-1α and IL-1β to thereby obtain the dual specificity antibody, wherein said antibody is not a fully mouse antibody.

9. (Amended) The method of claim 4, wherein the antigen is ~~designed based on~~ made by splicing together overlapping portions of IL-1α and IL-1β to create a hybrid molecule.

31. (Amended) A dual-specificity antibody, or antigen-binding portion thereof, that specifically binds interleukin-1α and interleukin-1β, said dual-specificity antibody, or antigen-binding portion thereof obtainable by the method of claim 4.